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The combination of transcatheter arterial chemoembolisation (TACE) and thermal ablation versus TACE alone for hepatocellular carcinoma (Protocol)

Liu B, Chen H, Li W

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[Intervention Protocol]

The combination of transcatheter arterial chemoembolisation (TACE) and thermal ablation versus TACE alone for hepatocellular carcinoma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of the combination of TACE and thermal ablation compared with TACE alone in people with hepatocellular carcinoma.

BACKGROUND

Description of the condition

Hepatocellular carcinoma is the most predominant form of primary liver cancer, accounting for approximately 90% of occurrences, and it represents an increasing serious health problem worldwide (Mohd 2013; Laursen 2014; National Center for Health Statistics (US) 2015). The pathogenesis of hepatocellular carcinoma is a highly complex process which usually occurs in the context of liver cirrhosis, mainly involving chronic inflammation injury and the accumulation of genetic alterations (Schulze 2016). Hepatocellular carcinoma is the sixth most common cancer and the second most common cancer-related cause of death worldwide. Around 782,000 people are diagnosed and 746,000 die from hepatocellular carcinoma every year worldwide, with China accounting for about 50% of the total number of cancers and deaths (Torre 2015; Forner 2018). The incidence of hepatocellular carcinoma varies among different global regions. Approximately 80% of hepatocellular carcinomas occur in sub-Saharan Africa and eastern Asia, due to the high prevalence of hepatitis B virus infection and the intake of aflatoxin B1, with an incidence of over 20 per 100,000 individuals (El-Serag 2012). An intermediate hepatocellular carcinoma burden occurs in Mediterranean countries, with an incidence of 10 to 20 per 100,000 individuals. In America, the incidence is lower than 5 per 100,000 individuals (Mittal 2013). The main causes of hepatocellular carcinoma in Europe and America is hepatitis C virus infection and alcohol abuse (Trad 2017). Hepatocellular carcinoma incidence among men is four to eight times higher than among women (Yang 2014). Most hepatocellular carcinoma patients are older than 45 years (Llovet 2016).
The most prevalent staging system for hepatocellular carcinoma is The Barcelona Clinic Liver Cancer (BCLC) system which divides hepatocellular carcinoma into five stages based on the size

and number of tumours, vascular invasion, and liver function (EASL-EORTC 2012). The main risk factors are liver cirrhosis, infection with hepatitis B virus and C virus, intake of toxic substance (alcohol and aflatoxin B1), and metabolic syndromes (diabetes, obesity, non-alcoholic fatty liver disease, and hereditary haemochromatosis). Approximately 80% of hepatocellular carcinoma develops in people with liver cirrhosis (Kew 2014). The hepatocellular carcinoma mortality among men with a high baseline body mass index is five times higher than among men with a normal body mass index (Forner 2018). Other risk factors include age, tobacco use, and coinfection of human immunodeficiency virus. Diagnosis of hepatocellular carcinoma is confirmed by either histopathological biopsy or imaging techniques (ultrasound, contrast-enhanced computed tomography, or contrast-enhanced magnetic resonance imaging (MRI)) according to the current practice guideline of the American Association for the Study of Liver Diseases (Bruix 2011).

The treatment for hepatocellular carcinoma can be divided into curative therapies and palliative therapies. Resection, liver transplantation, and locoregional ablation are radical therapies with the curative intention of prolonging survival. However, only 20% of hepatocellular carcinoma patients, mostly diagnosed by regular screening, may gain survival benefit from resection and liver transplantation (Abdel-Rahman 2013). Curative ablation is recommended for patients with only two or three nodules which are less than 3 cm or a single nodule. The palliative therapies mainly involve transcatheter arterial chemoembolisation (TACE), sorafenib, and systemic treatment, with no or moderate survival benefits (Oliveri 2011; Chacko 2016).

Description of the intervention

In this review, we will focus on the combination of TACE and sequential thermal ablation therapy. During this combined therapy, TACE is performed firstly for all baseline tumours, followed by thermal ablation on all baseline tumours or only tumours that remain active after TACE. Baseline tumours refer to all active tumours before TACE. Active tumours are defined as 'living' tumours, which show characteristic vascular features of hepatocellular carcinoma - arterial hypervascularisation with washout in the portal venous system or the late phase at contrast-enhanced computed tomography, or contrast-enhanced MRI.

TACE is the most common treatment for hepatocellular carcinoma, which is recommended as the first-line treatment for intermediate stage hepatocellular carcinoma, according to the BCLC staging system (EASL-EORTC 2012). The mechanism of TACE consists of the injection of chemotherapeutic drugs, lipiodol and vascular occlusive agents into the hepatic artery; these can inhibit tumour growth, promote cell death, and maybe prolong survival (Oliveri 2011). The rationale for TACE is based on the concept that most of the blood supply of intrahepatic tumours is provided by the hepatic artery, while 75% of the blood flow of the normal liver parenchyma is supplied by the portal vein (Vogl 2003). Therefore, TACE can lead to selective necrosis of the liver tumour while it hardly affects normal liver parenchyma (Jaeger 1996). Alternatively, TACE can also be used to downsize a tumour or as a bridge to liver transplantation (Martin 2015).

Thermal ablation refers to the ablation therapies that induce irreversible cellular injury of tumour cells through heat mechanisms or cold mechanisms. Most kinds of ablation therapies are performed using a percutaneous approach, under real-time contrast-enhanced computed tomography, dynamic MRI, or ultrasound guidance. A puncture needle is used to lead the electrode into the target. After setting appropriate output power and duration, the electrode begins to produce heat or cold to surrounding tissue to induce complete necrosis (Ahmed 2011).

There are five main kinds of thermal ablation: radiofrequency ablation, microwave ablation, cryoablation, laser ablation, and ultrasound ablation (Goldberg 2003).

Radiofrequency ablation is the most widely used and the most well-studied thermal ablation, and is regarded as the standard therapy for BCLC A tumours which are not suitable for surgery (EASL-EORTC 2012). It has been proved to have a therapeutic efficacy similar to that of surgical resection or liver transplantation for hepatocellular carcinoma with a diameter within 3 cm (Zhu 2016). Radiofrequency ablation can induce complete necrosis of surrounding tissue by generating heat. The radiofrequency ablation technique also serves as a model for exploring the use of thermal ablation in clinical practice.

Microwave ablation can induce tumour cell death by microwave heating, which is generated by dielectric hysteresis (Ahmed 2011). Microwave ablation can reduce tumour tissue in a more efficient way by producing faster heating and higher temperatures compared to radiofrequency ablation (Brace 2007; Yang 2007). Furthermore, microwave ablation, compared to radiofrequency ablation, has better performance on overcoming heat sink effect (Ahmed 2011). However, microwave ablation is still a novel ablation technique; more details should be explored in further clinical practice.

Laser ablation is an ablative therapy that can induce electromagnetic heating to increase tissue temperatures to lethal levels by laser beam and results in complete necrosis of surrounding tissue (Ahmed 2011).

Ultrasound ablation therapy can concentrate intersecting beams of ultrasound on a target tumour through an acoustic lens and thus induce irreversible damage (Zhu 2013).

Cryoablation destroys cells by the application of alternating freezing and thawing to induce irreversible cellular injury (Awad 2009; Song 2016).

How the intervention might work

TACE is a palliative therapy, with a tumour response rate of 24% to 53% (Yang 2009). Generally, several sessions of TACE are needed

to achieve a high necrosis rate and local tumour control(Satake 2008). Due to high toxicity and adverse effects of chemotherapeutic agents, repeated TACE may result in liver failure (Li 2010). Besides, the incomplete necrosis of the tumour after TACE may cause intrahepatic recurrence of malignancy (Wu 2005).

Thermal ablation is a minimally invasive and curative therapy, with a complete necrosis rate of 76% to 100% for small hepatocellular carcinoma(Morimoto 2010); and 30% to 70% for larger hepatocellular carcinoma (Livraghi 2000). In patients with early-stage hepatocellular carcinoma (BCLC 0 or A) who are not suitable for resection, ablation therapy achieved five-year survival rates of 50% to 70% (EASL-EORTC 2012). The main advantages of thermal ablation include effective tumour ablation, preservation of maximal normal liver parenchyma, and low rates of complications (Yang 2009). The introduction of the mechanism of five types of thermal ablation therapies is shown below.

During radiofrequency ablation, an electrical circuit is created between a radiofrequency probe, the patient, and the grounding pads (Ahmed 2011). The alternating current leads to frictional agitation at the ionic level and heat generation around the probe (Corwin 2001). Dehydration and subsequent carbonisation of surrounding tissues would occur when the temperature is above 100 °C (Poggi 2015).

Microwave ablation generates heat through a process known as dielectric hysteresis, in which polar molecules in tissue (primarily water) are forced to continuously realign with the oscillating electric field (Lubner 2013). Thus, the kinetic energy of reformed molecules and the temperature of tissue increase. Microwave power can produce extremely high temperatures (> 150 °C) and induce necrosis of tissue (Brace 2007).

Laser ablation treats the tumour by irradiating it with a laser beam, which is an efficient and precise energy source for tissue heating (Ahmed 2011).

Ultrasound ablation is a non-invasive therapy. The main mechanism of ultrasound ablation is the thermal energy deposition by a focused ultrasound beam. The targeted tissue absorbs a significant amount of energy from a highly directional ultrasound beam, resulting in elevation of temperature (Wijlemans 2012).

Cryoablation is an ablative technique which can induce protein denaturation, cellular dehydration and subsequent tissue necrosis by the application of extreme low temperatures to tumour tissue (Rubinsky 1990; Wu 2015).

The rationale of the combination of TACE and sequential ablation is that sequential ablation therapy can remedy the limitation of TACE alone. Firstly, ablation therapy can directly destroy tumour tissue, increase complete necrosis rate and produce a favourable prognosis (Li 2010); secondly, sequential ablation therapy reduces the time needed for interventional treatment, which reduces liver damage and improves quality of life (Li 2016). In addition, the combination of TACE and sequential ablation has synergistic effects on treating liver tumours. The occlusion of hepatic arteries achieved by TACE can reduce blood flow and decrease the heat sink effect, which is helpful for enlarging the ablation zone and achieving complete necrosis (Peng 2013).

Why it is important to do this review

Hepatic resection is regarded as the curative therapy for hepatocellular carcinoma. However, only about 20% of hepatocellular carcinoma patients are candidates for resection, which highlights the importance of effective non-surgical therapies (Yin 2014). Until now, TACE is the most commonly used palliative therapy for hepatocellular carcinoma, but the effect remains unsatisfactory (Oliveri 2011). In recent years, the combination of TACE and thermal ablation has shown better survival than TACE alone for people with hepatocellular carcinoma. Some studies have reported that the combination modality can confer a more favourable prognosis than TACE alone for different stages of hepatocellular carcinoma (Yang 2009; Azuma 2016; Hyun 2016; Song 2016). However, there is still a lack of clear and compelling evidence to prove the beneficial or harmful effect of the combination of TACE and thermal ablation therapy. Therefore, we want to conduct a Cochrane Review, with an intention to provide the best level of evidence for the role of the combination of TACE and thermal ablation versus TACE alone for hepatocellular carcinoma.

OBJECTIVES

To assess the beneficial and harmful effects of the combination of TACE and thermal ablation compared with TACE alone in people with hepatocellular carcinoma.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical trials comparing the combination of TACE and thermal ablation with TACE alone for hepatocellular carcinoma, irrespective of the language, publication status, or blinding. During the selection of trials, if we identify observational studies (i.e. quasi-randomised studies, cohort studies, case-control studies, case reports, and case series) retrieved with the searches for randomised clinical trials, we will include these studies for separate evaluation of harms only. By choosing this strategy, we are aware that we will put more focus on potential benefits and may overlook late-occurring or rare harms which are often missed in randomised clinical trials (Storebø 2018). If

we demonstrate clear benefits of the combination of TACE and thermal ablation, then we need to conduct systematic reviews of harms in observational studies. We will not analyse the extracted data on harms from non-randomised clinical studies together with the data on harms from the included randomised clinical trials; neither will we assess the bias risk in these studies. However, at the end of the Results section we will refer to the extracted narrative data on harm with a link to the table in the Appendices section or we may present a narrative analysis.

Types of participants

All trial participants older than 18 years, with hepatocellular carcinoma, diagnosed by either histopathological biopsy or the current practice guidelines of the American Association for the Study of Liver Disease.

Types of interventions

Experimental intervention

A combination of TACE and thermal ablation. Thermal ablation includes five kinds of ablation technique: radiofrequency ablation (Ahmed 2011), microwave ablation (Brace 2007; Lubner 2013; Poggi 2015), laser ablation (Ahmed 2011), ultrasound ablation (Wijlemans 2012), and cryoablation (Rubinsky 1990; Ahmed 2011)

Control intervention

TACE alone. For both experimental group and control group, we will include all TACE therapy irrespective of dosage and types of chemotherapeutic drugs and vascular occlusive agents (Imai 2014).

Types of outcome measures

Primary outcomes

- All-cause mortality at maximal follow-up. As exploratory analysis, we will also estimate the intervention effect at 1, 3, and 5 (primary time point) years
- Progression-free survival (PFS). The definition of PFS is the period from the date of first treatment to the date of the first documented disease progression by either radiological assessment or liver biopsy or death caused by any reason, whichever happened first.
- Proportion of participants with serious adverse events (SAEs). We will use the definition of SAEs in the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH-GCP 1997): that is, any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or any medical event that might have jeopardised the patient, or required intervention to prevent it. All other adverse events will be considered as non-SAEs. We will accept all reported SAEs assessed at variable time points throughout the conduct of the review. We will note the period of reported SAEs and classify them as short-term (primary observed period) and long-term SAEs.

Secondary outcomes

- Tumour response. We will evaluate the tumour response according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) guideline (Lencioni 2010), as follows.
    - Complete response (CR): disappearance of any intratumoural arterial enhancement in all target lesions.
    - Partial response (PR): at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
    - Progressive disease (PD): an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.
    - Stable disease (SD): any cases that do not qualify for either partial response or progressive disease.

Whenever appropriate we will also consider the disease response evaluation criteria of the European Association for the Study of the Liver (Bruix 2001), and the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Therasse 2000). However, mRECIST guideline will be considered as the main tool.

- Proportion of participants with adverse events not considered serious. We will accept all reported adverse events assessed at variable time points throughout the conduct of the review. We will note the period of reported adverse events and classify them as short-term (primary observed period) and long-term adverse events.
- Health-related quality of life as defined by the trial authors (short term: up to 1 year; medium term: 1 to 5 years; long-term (primary time point): beyond 5 years).

Exploratory outcomes

- Duration of hospital stay.

Search methods for identification of studies

Electronic searches

We will perform electronic searches in the following databases: The Cochrane Hepato-Biliary Group Controlled Trials Register (Cochrane Hepato-Biliary Group Module), The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane

Library, MEDLINE (PubMed), Embase (www.embase.com), LILACS (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index - Science (Web of Science) (Royle 2003). We will also endeavour to identify relevant randomised clinical trials in the China National Knowledge Infrastructure (CNKI) and Wanfang databases. Appendix 1 shows the preliminary search strategies with the expected time spans of the searches. At review stage, we will improve the search strategies if necessary.

Searching other resources

We will check the reference lists of potentially relevant articles identified in the electronic searches. We also will search online trial registries, such as ClinicalTrials.gov, Chinese Clinical Trial Register (ChiCTR), and the World Health Organization (WHO) International Clinical Trial Registry Platform (www.who.int/ictrp), for any ongoing studies. We will also handsearch grey literature sources, such as meeting abstracts and internal reports. We will adapt the same or similar search terms to those used in the searching of English electronic databases.

Data collection and analysis

Selection of studies

We will merge all search results and remove duplicates by using a reference management software. Two review authors (BZL and WL) will independently examine titles and abstracts of electronic search output to remove obviously irrelevant reports. After the initial assessment, we will retrieve the full text of all potentially eligible articles and we will link together multiple reports of the same study. Then two review authors (BZL and WL) will independently screen the full text to evaluate whether these trials meet the inclusion criteria. We will resolve disagreement on the eligibility of a study by discussion. We will consult HC (the last review author) or we will write to the original trial investigators if necessary to clarify study eligibility. We will then make a final decision. During the whole selection process we will not be blind to information relating to articles. We will record the details of the whole screening process by completing a PRISMA flow chart and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two authors (BZL and WL) will independently extract the data from all included articles and complete the 'Characteristics of included studies' table. We will contact the authors of original trials in case of missing data. We will resolve disagreement by discussion. We will consult HC (the last review author) or we will write to the original trial investigators if necessary. Two authors (HC and WL) will enter data into Review Manager 5. We will double-check that the data have been entered correctly by comparing the data presented in the systematic review with that in the data extraction form, which we will pre-pilot for the purpose of the review.
We will extract the following study characteristics.

- Source (e.g. author, year of publication, contact details, journal citation)
- Methods (e.g. study design, total study duration, sequence generation, allocation sequence concealment, blinding and other concerns about bias)
- Participants (e.g. age, sex, country, number randomised, number lost to follow-up/withdrawn, number analysed, inclusion criteria, exclusion criteria, diagnostic criteria)
- Interventions (e.g. intervention, comparison)
- Outcomes (for each outcome listed in the protocol, e.g. outcome definition and unit of measurement (if relevant), time points reported, scales, intensity)
- Miscellaneous (e.g. funding for trial, a notable conflicts of interest of trial authors)

Assessment of risk of bias in included studies

Two review authors (BZL and WL) will independently assess the risk of bias in the included studies. We will assess risk of bias according to the Cochrane 'Risk of bias' tool (Higgins 2011), the Cochrane Hepato-Biliary Group Module, and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Savović 2018), using the following domains with definitions.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Uncertain risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of or during enrolment. Allocation was controlled by a central and independent randomisation unit; or the allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Uncertain risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of or during enrolment.

- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants and personnel

- Low risk of bias - any of the following: blinding of participants and key study personnel ensured, and it was unlikely that the blinding could have been broken; or (rarely) no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding.
- Unclear risk of bias - any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias - any of the following: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias - any of the following: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken; or (rarely) no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding.
- Unclear risk of bias - any of the following: insufficient information to permit judgement of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias - any of the following: no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported all-cause mortality, hepatocellular carcinoma-related morbidity, and serious adverse events. If the original trial protocol was available, the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.ClinicalTrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we will not consider those outcomes to be reliable.
- Unclear risk of bias: the study authors did not report all predefined outcomes fully, or it was unclear whether the study authors recorded data on these outcomes or not.
- High risk of bias: the study authors did not report one or more predefined outcomes.

Other bias

- Low risk of bias: the trial appeared free of other factors that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.

Overall risk of bias

We will assess overall risk of bias in the trials as:

- low risk of bias: if all the bias domains described in the above paragraphs are classified as low risk of bias;
- high risk of bias: if one or more of the bias domains described in the above paragraphs are classified as 'unclear risk of bias' or 'high risk of bias'.

We will assess the domains 'Blinding of outcome assessment', 'Incomplete outcome data', and 'Selective outcome reporting' for each outcome. Thus, we will be able to assess the bias risk for each outcome in addition to each trial.
We will base our primary conclusions and our presentation in the 'Summary of findings' table on the results of our primary outcomes at low risk of bias.

Measures of treatment effect

For dichotomous variables, we will calculate risk ratio (RR) and 95% confidence intervals (CI) and Trial Sequential Analysis adjusted-CI.
For continuous variables, we will use the mean difference (MD) (if all studies were made on the same scale) or the standardised mean difference (SMD) (if different scales were used) with 95% CI and Trial Sequential Analysis adjusted-CI.

For time-to-event variables, we will use the methods of survival analysis and express the intervention effect as a hazard ratio (HR) with 95% Cl. When the log HR and their variance are not directly reported in reports we will calculate them indirectly, following the methods introduced by Tierney 2007.

Unit of analysis issues

We will analyse cluster-randomised trials using the average cluster size and an estimate of the intraclass correlation coefficient (ICC) and the design effect to calculate effective sample size. This process will follow the method introduced in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will acknowledge any possible heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate possible effects of the randomisation unit.

For studies with multiple intervention groups, we will combine all relevant experimental intervention groups of the study into a single group, and combine all relevant control intervention groups into a single control group, to create a single pair-wise comparison.

Dealing with missing data

We will try to contact the original investigators to request missing data; and we will extract all data for an intention-to-treat (ITT) analysis if data are available. Otherwise we will perform available case analyses, which assume that data are missing at random. We will assess if this assumption is reasonable by collecting data on the number of participants excluded or lost to follow-up, and the reasons for loss to follow-up by treatment group, from each included study (as reported). We will address the potential impact of missing data on the findings of the review in the Discussion section. If the trial authors provide it we will use imputed data, using a robust method; however, we will not directly impute data ourselves.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of the included trials. We will assess the presence of clinical heterogeneity by comparing effect estimates in people with and without cirrhosis, aetiology of hepatocellular carcinoma, and liver function (Child-Pugh class). Different study designs and risk of bias may contribute to methodological heterogeneity.

We will explore statistical heterogeneity by the Chi² test with significance set at a P value of less than 0.10. In addition, we will access the degree of heterogeneity by using the I² statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error.

Interpretation of I² is listed as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity*
- 50% to 90%: may represent substantial heterogeneity*
- 75% to 100%: considerable heterogeneity*

*The importance of the observed value of I² depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi² test, or a confidence interval for I²).

Assessment of reporting biases

We will assess reporting bias by drawing funnel plots if 10 or more trials are included.

Data synthesis

Meta-analysis

We will conduct this review following the instructions stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary Group Module, and the eight-step procedure for validation of meta-analytic results in systematic reviews as suggested by Jakobsen 2014. We will use meta-analyses whenever it is possible. Otherwise, we will provide a summary of the study results in a narrative way. We will analyse data using the Review Manager 5 software provided by Cochrane (Review Manager 2014). If it is assumed that each study is estimating exactly the same quantity, we will perform a fixed-effect meta-analysis. Otherwise, we will use a random-effects model.

Trial Sequential Analysis

To control random errors from sparse data and repeated significance testing, we will apply Trial Sequential Analysis in our meta-analysis (Thorlund 2011; TSA 2011), for both primary outcomes and second outcomes (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). Trial Sequential Analysis is a methodology that includes a combination of techniques, providing the threshold for a statistically significant treatment effect and the threshold for futility. Conclusions conducted by Trial Sequential Analysis indicate the potential to be more reliable than those using traditional meta-analysis techniques (Thorlund 2011).

For dichotomous outcomes, we will calculate the required meta-analysis information size based on the event proportion in the control group; assumption of a plausible RR reduction of 20% or the RR reduction observed in the included trials at low risk of bias; a risk of type I error of 2.5% because of our three primary outcomes and 2.5% because of three secondary outcomes (Jakobsen 2014); a risk of type II error of 10%; and the assumed diversity of the meta-analysis (Wetterslev 2009). For continuous outcomes, we will calculate the required information size based on the SD observed in the control group of trials with low risk of bias and a

minimal relevant difference of 50% of this SD, an alpha of 2.5%, a beta of 10%, and the diversity suggested by the trials in the meta-analysis.

The underlying assumption of Trial Sequential Analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We will add the trials according to the year of publication. If more than one trial is published during the same year, we will add trials alphabetically according to the last name of the first author. We will construct trial sequential monitoring boundaries on the basis of the required information size (Wetterslev 2008; Thorlund 2011). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that does not reach the required information size; if the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may perhaps have been established and further trials may be superfluous. On the other hand, if the boundaries are not surpassed, it will probably be necessary to continue conducting trials in order to detect or reject a certain intervention effect. That is determined by assessing if the cumulative Z-curve crosses the trial sequential boundaries for futility.

Trial Sequential Analysis will act as our sensitivity analysis for the assessment of imprecision with GRADE (see below).

Subgroup analysis and investigation of heterogeneity

We will assess differences between subgroups using the formal test for subgroup differences in Review Manager 5 (Review Manager 2014). We will conduct the following subgroup analyses.

- Trials at low risk of bias compared to trials at high risk of bias.
- Trials at risk of vested interests compared to trials at no risks of vested interest.
- Different ablation methods.
- Trial participants at different BCLC stages.
- Trial participants at different Child-Pugh Class cirrhosis.
- Trials up to the median follow-up compared to trials at or exceeding median follow-up.

Sensitivity analysis

In addition to Dealing with missing data, we will also compare our assessments of imprecision in the included trials, performed by GRADE and TSA, for each of the Primary outcomes and Secondary outcomes (Castellini 2018; Gartlehner 2018).

'Summary of findings' tables

We will create the 'Summary of findings' tables by using GRADEpro GDT software (GRADEpro 2015). We will assess all-cause mortality, progression-free survival at the longest follow-up, serious adverse events, tumour response; events considered non-serious adverse events; and health-related quality of life. We will use the GRADE approach to assess the quality of evidence based on risk of bias, indirectness of evidence (population, intervention, control, outcomes), unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses), imprecision of results, and a high probability of publication bias (Atkins 2004). We will define the levels of evidence as 'high', 'moderate', 'low' or 'very low' certainty. These grades are defined as follows.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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Peer reviewers: Karl Heinz Weiss, Germany.

Contact editor: Stefano Trastulli, Italy.

Sign-off editor: Christian Gluud, Denmark.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search Strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be provided at review stage.	(((hepat* or liver) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or hepatocellular caricoma or HCC) AND (((thermal or (radiofrequenc* or radio-frequenc* or radio frequenc*) or microwave or laser* or high intensity focused ultrasound or cryo*) AND (ablati* or therap* or treat* or suger* or coag*)) OR cryoablati* or cryosuger* or RFA or RFTA or RFT or RFCA or MWA or HIFU) AND (((transcatheter or transarterial) and chemoemboli*) or TACE)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Carcinoma, Hepatocellular] explode all trees #2 MeSH descriptor: [Liver Neoplasms] explode all trees #3 (((hepat* or liver) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or hepatocellular caricoma or HCC) #4 #1 or #2 or #3 #5 MeSH descriptor: [Catheter Ablation] explode all trees #6 MeSH descriptor: [Ablation Techniques] explode all trees #7 MeSH descriptor: [Cryosurgery] explode all trees #8 MeSH descriptor: [Laser Therapy] explode all trees #9 MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees #10 ((thermal or (radiofrequenc* or radio-frequenc* or radio frequenc*) or microwave or laser* or high intensity focused ultrasound or cryo*) AND (ablati* or therap* or treat* or

(*Continued*)

		suger* or coag*)) OR cryoablati* or cryosuger* or RFA or RFTA or RFT or RFCA or MWA or HIFU #11 #5 or #6 or #7or #8 or #9 or #10 #12 MeSH descriptor [Embolization, Therapeutic] explode all trees #13 ((transcatheter or transarterial) and chemoemboli*) orTACE #14 #12 or #13 #15 #4 and #11 and #14 in trials
MEDLINE (PubMed)	1946 to the date of search	((((hepatocellular OR hepato-cellular OR hepatic OR liver) and (carcinom* OR cancer OR neoplasm* OR malign* OR tumor)) OR hepatocellular carcinoma OR HCC) OR Carcinoma, Hepatocellular[MeSH] OR Liver Neoplasms[MeSH]) and ((((thermal OR (radiofrequenc* OR radio-frequenc* OR radio frequenc*) OR microwave OR laser OR high intensity focused ultrasound) AND (ablati* OR therapy OR therapies OR treat* OR suger* OR coag*)) OR cryoablati* OR RFA OR rfta OR RFT OR rfca OR MWA OR hifu) OR Catheter Ablation[MeSH] OR Ablation Techniques[MeSH] OR Cryosurgery[MeSH] OR Laser Therapy[MeSH] OR High Intensity Focused Ultrasound Ablation[MeSH]) and (((transcatheter OR transarterial) and chemoemboli*) OR TACE) OR Chemoembolization, Therapeutic[MeSH]) and ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh]))
Embase (www.embase.com)	1974 to the date of search	#1 'liver cell carcinoma'/exp #2 ((hepat* or liver) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or 'hepatocellular caricoma' or HCC #3 #1 or #2 #4 'radiofrequency ablation'/exp #5 'catheter ablation'/exp #6 'microwave thermotherapy'/exp #7 'cryoablation'/exp #8 'laser surgery'/exp #9 'high intensity focused ultrasound'/exp #10 thermal or (radiofrequenc* or radio-frequenc* or radio frequenc*) or microwave or

(*Continued*)

		laser* or 'high intensity focused ultrasound' or cryo* #11 ablation* or therap* or treat* or suger* or coag* #12 #10 and #11 #13 cryoablati* or cryosuger* or RFA or RFTA or RFT or RFCA or MWA or HIFU #14 #4 or #5 or #6 or #7 or #8 or #9 or #12 or #13 #15 'chemoembolization'/exp #16 ((transcatheter or transarterial) and chemoemboli*) or TACE #17 #15 or #16 #18 #3 and #14 and #17 #19 random* or blind* or placebo* or 'meta-analysis' #20 #18 and #19
LILACS (Bireme)	1982 to the date of search	(((hepat$ or liver) and (carcinom$ or cancer$ or neoplasm$ or malign$ or tumo$)) or hepatocellular caricoma or HCC) AND (((thermal or (radiofrequenc$ or radio-frequenc$ or radio frequenc$) or microwave or laser$ or high intensity focused ultrasound or cryo$) [Words] and (ablati$ or therap$ or treat$ or suger$ or coag$)) OR cryoablati$ or cryosuger$ or RFA or RFTA or RFT or RFCA or MWA or HIFU) [Words] and (((transcatheter or transarterial) and chemoemboli$) or TACE) [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of search	#1 TS=(((hepat* or liver) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or hepatocellular caricoma or HCC) #2 TS=(thermal or (radiofrequenc* or radio-frequenc* or radio frequenc*) or microwave or laser* or high intensity focused ultrasound or cryo*) #3 TS=(ablati* or therap* or treat* or suger* or coag*) #4 #2 AND #3 #5 TS=(cryoablati* or cryosuger* or RFA or RFTA or RFT or RFCA or MWA or HIFU) #6 #4 OR #5 #7 TS=(((transcatheter or transarterial) and chemoemboli*) or TACE) #8 TS=(random* OR blind* OR placebo* OR meta-analysis) #9 #1 AND #6 AND #7 AND #8

(*Continued*)

Conference Proceedings Citation Index - Science (Web of Science)	1990 to the date of search	#1 TS=(((hepat* or liver) and (carcinom* or cancer* or neoplasm* or malign* or tumo*)) or hepatocellular caricoma or HCC) #2 TS=(thermal or (radiofrequenc* or radio-frequenc* or radio frequenc*) or microwave or laser* or high intensity focused ultrasound or cryo*) #3 TS=(ablati* or therap* or treat* or suger* or coag*) #4 #2 AND #3 #5 TS=(cryoablati* or cryosuger* or RFA or RFTA or RFT or RFCA or MWA or HIFU) #6 #4 OR #5 #7 TS=(((transcatheter or transarterial) and chemoemboli*) or TACE) #8 TS=(random* OR blind* OR placebo* OR meta-analysis) #9 #1 AND #6 AND #7 AND #8
China National Knowledge Infrastructure	Date will be provided at review stage.	TI=('TACE' + '肝动脉化疗栓塞' + '栓塞') AND TI=('热消融' + '消融' + '射频消融' + 'RFA' + '微波消融' + 'MWA' + '氩氦刀消融' + '冷冻消融' + 'HIFU' + '高强度聚焦超声' + '超声消融' + '激光消融') AND TI=('肝癌' + '肝细胞癌') AND (AB=('随机' + '随机对照') OR FT=('随机' + '随机对照'))
Wanfang	Date will be provided at review stage.	主题: (TACE + "肝动脉栓塞" + "肝动脉化疗栓塞") * ("热消融" + "射频消融" + RFA + "微波消融" + MWA + "氩氦刀消融" + "冷冻消融" + HIFU + "高强度聚焦超声" + "超声消融" + "激光消融") * ("肝癌" + "肝细胞癌") * ("随机" + "随机对照")

CONTRIBUTIONS OF AUTHORS

Formulated the research question: WL

Drafted the protocol: BZL and WL

Provision of statistical expert opinion: HC

All authors approved the publication of the current version.

DECLARATIONS OF INTEREST

BZL has no known conflicts of interest.

HC has no known conflicts of interest.

WL has no known conflicts of interest.

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